An Open-label Randomized Phase III Trial of BMS-936558 versus Docetaxel in Previously Treated Advanced or Metastatic Squamous Cell Non-small Cell Lung Cancer (NSCLC)

Published: 24-07-2012
Last updated: 30-04-2024

Primary ObjectiveTo compare the objective response rate and overall surival of BMS-936558 versus docetaxel in subjects with squamous cell NSCLC after failure of prior platinum-based chemotherapySecondary ObjectivesTo compare the progression-free...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Metastases
Study type	Interventional

Summary

ID

NL-OMON37458

Source
ToetsingOnline

Brief title
CA209-017

Condition

- Metastases
- Respiratory tract neoplasms

Synonym
Squamous cell non small cell lung cancer

Research involving
Human

Sponsors and support

Primary sponsor: Bristol-Myers Squibb
Source(s) of monetary or material Support: Pharmaceutical industry

Intervention

Keyword: BMS-936558, Docetaxel, Squamous cell non-small cell lung cancer

Outcome measures

Primary outcome

The primary objective in the study will be measured by the co-primary endpoints of Objective Response Rate (ORR) and overall survival (OS).

The ORR is defined as the number of subjects with a best overall response (BOR) of complete response (CR) or partial response (PR) divided by the number of randomized subjects. OS is defined as the time from randomization to the date of death. A subject who has not

died will be censored at last known date alive. OS will be followed

continuously while subjects are on the study drug and every 3 months via

in-person or phone contact after subjects discontinue the study drug.

Secondary outcome

The first secondary objective (to compare progression free survival PFS as assessed by the independent review committee,IRC) will be measured by the key secondary endpoint PFS in each randomized arm. It is defined as the time from randomization to the date of the first documented tumor progression as determined by the IRC (per RECIST 1.1), or death due to any cause. Subjects who die without a

reported prior progression will be considered to have progressed on the date of

their death. Subjects who did not progress or die will be censored on the date of their last evaluable tumor assessment. Subjects who did not have any on study tumor assessments
and did not die will be censored on the date they were randomized. Subjects who started any subsequent anti-cancer therapy without a prior reported progression will be censored at the last evaluable tumor assessment prior to initiation of the subsequent anti-cancer therapy.

The second secondary objective (to evaluate clinical benefit in PD-L1+ and PD-L1- subgroups) will be measured by the same primary endpoints. ie, ORR and OS in subjects within PD-L1+ and PD-L1- subgroups.

The third secondary objective (to evaluate durability of and time to objective response) will be measured by secondary endpoints duration of objective response (DOOR) and time to objective response (TTOR) in each randomized arm. DOOR is defined as the time
between the date of first response to the date of the first documented tumor progression (per RECIST 1.1) or death due to any cause. Subjects who neither progress nor die will be censored on the date of their last assessment. TTOR is defined as the time from randomization to the date of the first documented CR or PR. DOOR and TTOR will be evaluated for responders (CR or PR) only.

The fourth secondary endpoint (to evaluate quality of life) will be measured by secondary endpoint of disease-related symptom progression rate. It is defined

as the proportion of randomized subjects who had a disease-related symptom progression as measured by the lung cancer symptom scale, LCSS. The first six items of the LCSS are summarized into a symptom scale ranging in score from zero (0) to one hundred (100), with zero being the best possible score and 100 the worst possible score. LCSS questionnaire is completed on Day 1 of the scheduled cycle for the first 6 months on study treatment, then every 6 weeks thereafter for the remainder of the study, and at the first two follow-up visits.

Study description

Background summary

Therapeutic options for squamous cell NSCLC are particularly limited after failure of front line chemotherapy. Therefore, while representing a minority of NSCLC cases, squamous cell NSCLC remains a disease with high burden and unmet medical need.
Substantial monotherapy clinical activity has been observed in >= second line NSCLC subjects treated in the ongoing Phase 1 study of BMS-936558 (CA209003), and in particular in subjects with squamous cell NSCLC, This study showed objective response rates (ORR) greater than the historical ORR for docetaxel (approximately 8-10%). Preliminary estimates of median duration of response for NSCLC subjects in CA209003 approached 6 months, indicating response durability. Conversely, the historical median PFS for docetaxel is approximately 3 months. The clinical activity of BMS-936558 observed to date in squamous cell NSCLC suggests the potential for improved clinical outcomes as monotherapy. However, the potential benefit over standard of care docetaxel is not yet known.Docetaxel was therefore chosen as the comparator for this study, due to its clinical activity and lack of other suitable second line options in subjects with squamous cell NSCLC.
Docetaxel has a well characterized adverse event profile consistent with cytotoxic chemotherapy, including the potential for serious pancytopenia, fluid retention, peripheral neuropathies, asthenia, diarrhoea, nausea and vomiting. BMS-936558 also has the potential for clinically relevant adverse events including liver toxicities, thyroiditis, pneumonitis, and diarrhoea. However, the activity and manageable AEs profile observed with BMS-936558 supports a head-to-head evaluation versus

docetaxel in second-line squamous cell NSCLC.

Study objective

Primary Objective
To compare the objective response rate and overall surival of BMS-936558 versus docetaxel in subjects with squamous cell NSCLC after failure of prior platinum-based chemotherapy

Secondary Objectives
To compare the progression-free survival (PFS) of BMS-936558 versus docetaxel
• To evaluate clinical benefit in terms of ORR and OS of BMS-936558 versus docetaxel, in PD-L1+ versus PD-L1- protein expression subgroups
• To evaluate durability of and time to objective response in BMS-936558 and docetaxel groups
• To evaluate the proportion of subjects exhibiting disease-related symptom progression, as measured by LCSS, in BMS-936558 and docetaxel groups

Exploratory Objectives
• To assess the overall safety and tolerability of BMS-936558 versus docetaxel
• To explore potential predictive biomarkers of BMS-936558 efficacy (such as ORR, PFS and OS) in peripheral blood and tumor specimens, including antibodies to tumor antigens and proteins involved in regulating immune responses (eg PD-1, PD-L1, PDL2)
• To assess the effects natural variation single nucleotide polymorphism (SNPs) in select genes (eg PD-1, PD-L1, PD-L2, CTLA-4) has on clinical endpoints and/or on the occurrence of adverse events
• To characterize pharmacokinetics of BMS-936558 and explore exposure-response (exposure-safety and exposure-efficacy) relationships with respect to selected safety and efficacy endpoints
• To characterize immunogenicity of BMS-936558
• To assess the subject*s overall health status using the EQ-5D Index and visual analog scale.

Study design

This is a randomized open-label Phase 3 study in adult (>= 18 years old) male and female subjects with advanced or metastatic squamous cell NSCLC after failure of prior platinum-doublet chemotherapy. Subjects will undergo screening evaluations to determine eligibility within 28 days prior to randomization. Subjects will be assigned to one of two treatment arms, BMS-936558 (3 mg/kg every 2 weeks) or docetaxel (75 mg/m3 every 3 weeks). Randomization will be stratified and balanced according to the following factors: prior paclitaxel vs. no paclitaxel and region (US vs Europe vs Rest of World). Treatment should be initiated within 3 days of randomization. BMS-936558 or docetaxel will be administered as an IV infusion over 60 minutes on Treatment Day 1. A treatment

cycle is defined as 2 weeks for BMS-936558 and 3 weeks for docetaxel.
This study will consist of 3 phases: screening (up to 28 days), treatment and follow-up. Treatment will continue until documented disease progression, there is discontinuation due to toxicity, withdrawal of consent, or the study ends. During the follow-up phase, subjects will have 2 follow-up visits within the first 100 days from the last dose of therapy. Beyond 100 days from the last dose of study therapy, subjects will be followed for ongoing drug-related adverse events until resolved, return to baseline or deemed irreversible, or until lost to follow-up, withdrawal of study consent, or start of a subsequent anti-cancer therapy. This study will end when analysis of survival is complete. The duration of study will be approximately 2 years (24 months).

Intervention

The medicinal interventions for this trial include both BMS-936558 and docetaxel. Both compounds will be supplied by the Sponsor company.
Non investigational medicinal products for this trial include the premedication dexamethasone. Dexamethasone is being supplied by the Sponsor company and will be administered as per the guidelines of the hospital.
BMS-936558 is supplied as a solution at a potency of 100 mg (10 mg/mL) and docetaxel at a potency of 160 mg (20 mg/mL). BMS-936558 or docetaxel (depending on randomized treatment Arm) will be administered as an IV infusion over 60 minutes on Treatment Day 1. A treatment cycle is defined as 2 weeks for BMS-936558 and 3 weeks for docetaxel

Study burden and risks

As part of the trial, patients will be expected to attend multiple clinic visits where they will undergo physical examinations, vital sign measurements including oxygen saturation levels, blood tests for safety assessment, pregnancy testing (for females of child bearing potential) and monitoring for adverse events. In addition, every 6 weeks (from week 9 onwards) patients will undergo radiographic assessment of their tumour(s) (by CT or MRI) until disease progression or treatment discontinuation whichever occurs later. For those patients randomised to BMS-936558, blood samples will be collected at certain visits for research purposes (PK and immunogenicity). The frequency of visits and number of procedures carried out during this trial would typically be considered over and above standard of care.
Treatments for cancer often have side effects, including some that are life-threatening. Docetaxel has a well characterized adverse event profile consistent with cytotoxic chemotherapy, including the potential for serious pancytopenia, fluid retention, peripheral neuropathies, asthenia, diarrhea, nausea and vomiting. BMS-936558 also has the potential for clinically relevant adverse events including liver toxicities, thyroiditis, pneumonitis, and diarrhoea. However, the activity and manageable AEs profile observed with BMS-936558 supports a head-to-head evaluation versus docetaxel in second-line

squamous cell NSCLC. An independent Data Monitoring Committee (DMC) will be utilized to monitor the activity and safety of BMS-936558 versus docetaxel throughout the conduct of the trial.
The clinical activity of BMS-936558 observed to date in squamous cell NSCLC suggests the potential for improved clinical outcomes as monotherapy. There is an element of risk to the patients from the investigational medicinal products and procedures involved but this trial will answer an important medical question and provide data to demonstrate whether or not BMS-936558 improves overall survival over and above the standard chemotherapy agent, docetaxel. These procedures are carried by trained medical professionals and every effort will be made to minimise any risks or discomfort to the patient.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

1. Signed written informed consent
2. Men and women >= 18 years of age
3. Eastern Cooperative Oncology Group (ECOG) performance status of <= 1
4. Subjects with histologically or cytologically-documented squamous cell NSCLC who present with Stage IIIB/ Stage IV disease or recurrent disease following radiation therapy or surgical resection.
5. Subjects must have experienced disease recurrence or progression during or after one prior
platinum-containing doublet chemotherapy regimen for advanced or metastatic disease
a. Subjects who received erlotinib as maintenance therapy (non-progressors with platinum-based doublet chemotherapy) and progressed are eligible. However, subjects who received a tyrosine kinase inhibitor after failure of a prior platinum based therapy are excluded
b. Subjects who received adjuvant or neoadjuvant platinum-doublet chemotherapy (after surgery and/or radiation therapy) and developed recurrent or metastatic disease within 6 months of completing therapy are eligible.
c. Subjects with recurrent disease > 6 months after adjuvant or neoadjuvant platinum based chemotherapy, who also subsequently progressed during or after a platinum doublet regimen given to treat the recurrence, are eligible.
6. Subjects must have measurable disease by CT or MRI per RECIST 1.1 criteria; Radiographic Tumor Assessment performed within 28 days of randomization. Target lesions may be located in a previously irradiated field if there is documented (radiographic) disease progression in that site
7. A formalin fixed, paraffin-embedded (FFPE) tumor tissue block or unstained slides of tumor sample (archival or recent) must be available for biomarker evaluation. Biopsy should be excisional, incisional or core needle. Fine needle aspiration is insufficient.
8. Subjects must be willing and able to comply with scheduled visits, treatment schedule, laboratory tests including completion of patient reported outcomes questionnaires and other requirements of the study.
9. All baseline laboratory requirements will be assessed and should be obtained within -14 days of randomization. Screening laboratory values must meet the following criteria
i) WBCs >= 2000/µL
ii) Neutrophils >= 1500/µL
iii) Platelets >= 100 x 10^3/µL
iv) Hemoglobin >= 9.0 g/dL
v) Serum creatinine of <= 1.5 X ULN or creatinine clearance > 40 mL/minute (using Cockcroft/Gault formula)
vi) AST <= 1.5X ULN
vii) ALT <= 1.5X ULN
viii) Total bilirubin <= ULN (except subjects with Gilbert Syndrome who must have total bilirubin <3.0 mg/dL)
10. Prior radiotherapy or radiosurgery must have been completed at least 2 weeks prior to randomization
11. Women of childbearing potential (WOCBP) must use method(s) of contraception based on

the tables in Appendix 2 of the protocol. For a teratogenic study drug and/or when there is insufficient information to assess teratogenicity (preclinical studies have not been done), a highly effective method(s) of contraception (failure rate of less than 1% per year) is required. The individual methods of contraception should be determined in consultation with the investigator.
WOCBP must have a negative serum or urine pregnancy test within 24 hours prior to the start of investigational product.
Women must not be breastfeeding during the trial;12. Men who are sexually active with WOCBP must use any contraceptive method with a failure rate of less than 1% per year. The investigator shall review contraception methods and the time period that contraception must be followed.
Men that are sexually active with WOCBP must follow instructions for birth control for a period of 90 days plus the time required for the investigational drug to undergo five half lives.

Exclusion criteria

1. Subjects with active CNS metastases are excluded. Subjects are eligible if CNS mets are adequately treated and subjects are neurologically returned to baseline (except for residual signs or symptoms related to the CNS treatment) for at least 2 weeks prior to enrollment. In addition, subjects must be either off corticosteroids, or on a stable or decreasing dose of <= 10
mg daily prednisone (or equivalent).
2. Subjects with carcinomatous meningitis
3. Subjects with active, known or suspected autoimmune disease. Subjects with vitiligo, type I
diabetes mellitus, residual hypothyroidism due to autoimmune thyroiditis only requiring hormone replacement, or conditions not expected to recur in the absence of an external trigger
are permitted to enroll.
4. Subjects with a condition requiring systemic treatment with either corticosteroids (>10 mg daily prednisone equivalent) or other immunosuppressive medications within 14 days of randomization. Inhaled or topical steroids, and adrenal replacement steroid doses > 10 mg daily prednisone equivalent, are permitted in the absence of active autoimmune disease.
5. Prior therapy with anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-CTLA-4 antibody (including ipilimumab or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways).
6. Prior treatment on the first-line study CA184104
7. Prior treatment with docetaxel
8. Subjects with a history of interstitial lung disease
9. Other active malignancy requiring concurrent intervention
10. Subjects with previous malignancies (except non-melanoma skin cancers, and the following
in situ cancers: bladder, gastric, colon, endometrial, cervical/dysplasia, melanoma, or breast) are excluded unless a complete remission was achieved at least 2 years prior to study entry AND no additional therapy is required during the study period

11. Treatment with any investigational agent within 28 days of first administration of study treatment
12. All toxicities attributed to prior anti-cancer therapy other than alopecia and fatigue must have resolved to grade 1 (NCI CTCAE version 4) or baseline before administration of study drug.
13. Subjects must have recovered from the effects of major surgery or significant traumatic injury at least 14 days before the first dose of study treatment
14, Known history of testing positive for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome (AIDS).
15. Positive test for hepatitis B virus surface antigen (HBV sAg) or hepatitis C virus ribonucleic acid (HCV RNA) indicating acute or chronic infection.
16. History of severe hypersensitivity reactions to other monoclonal antibodies.
17. History of severe hypersensitivity reaction to prior paclitaxel
18. History of allergy or intolerance (unacceptable adverse event) to study drug components or Polysorbate-80-containing infusions.
19. WOCBP who are pregnant or breastfeeding
20. Women with a positive pregnancy test at enrolment or prior to administration of study medication
21. Ongoing or planned administration of anti-cancer therapies other than those specified in this study
22. Use of corticosteroids or other immunosuppressive medications as per Exclusion Criteria 2b
23. Strong CYP3A4 inhibitors (See Section 3.4.1 of the protocol)
24. Any other serious or uncontrolled medical disorder, active infection, physical exam finding, laboratory finding, altered mental status, or psychiatric condition that, in the opinion of the investigator, would limit a subject*s ability to comply with the study requirements, substantially increase risk to the subject, or impact the interpretability of study results
25. Prisoners or subjects who are involuntarily incarcerated
26. Subjects who are compulsorily detained for treatment of either a psychiatric or physical (e.g., infectious disease) illness

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active

Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	23-08-2012
Enrollment:	10
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	BMS-936558
Generic name:	BMS-936558
Product type:	Medicine
Brand name:	Taxotere
Generic name:	Docetaxel
Registration:	Yes - NL intended use

Ethics review

Approved WMO

Date:	24-07-2012
Application type:	First submission
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)

Approved WMO

Date:	23-08-2012
Application type:	First submission
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)

Approved WMO

Date:	30-10-2012
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)

Approved WMO

Date:	12-11-2012
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	10-06-2013
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	02-08-2013
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	23-08-2013
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	24-10-2013
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	04-12-2013
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	09-12-2013
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	15-07-2014
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van

	Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	31-07-2014
Application type:	Amendment
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Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	11-02-2015
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	15-04-2015
Application type:	Amendment
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Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
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Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	08-07-2016
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	19-10-2017
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Approved WMO Date:	20-10-2020
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2011-004792-36-NL
ClinicalTrials.gov	NCT01642004
CCMO	NL39969.031.12

Study results

Results posted: 30-08-2022

First publication
01-01-1900